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APPROVAL SHEET


Title of Dissertation: "Postconcussive Symptoms in OEF/OIF Veterans Presenting to a Polytrauma Clinic with a History of Traumatic Brain Injury"

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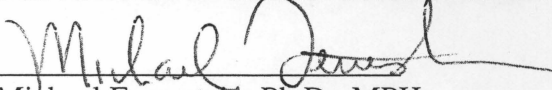
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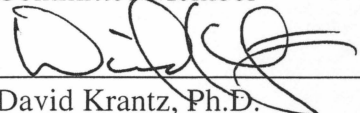


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A handwritten signature in black ink, appearing to read 'G. Zeckler', with a long horizontal flourish extending to the right.

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ABSTRACT

Title of Thesis: Postconcussive Symptoms in OEF/OIF Veterans Presenting to a Polytrauma Clinic with a History of Traumatic Brain Injury

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With the growing numbers of traumatic brain injuries (TBIs) occurring within the OIF/OEF combat theaters of operations, there is a greater need to identify clinical correlates of post-concussive symptoms (PCSx) within Veterans with a history of TBI. A retrospective record review was conducted within a group of OEF/OIF Veterans with TBI who completed a neuropsychological assessment. Differences in PCSx were examined by injury severity, number of TBIs sustained, and time since injury. Correlations of PCSx (Neurobehavioral Symptom Inventory scores) with self-report measures of mood, anxiety, and PTSD symptoms, neuropsychological test performance, and medical characteristics were examined. Higher levels of self-reported PCSx were related to mood, anxiety, and PTSD symptoms, prescription medications, and neurocognitive test measures of learning and recall. In conclusion, PCSx appear to be strongly related to psychiatric symptoms and other factors aside from specific TBI characteristics among treatment-seeking OEF/OIF Veterans with a history of TBI.

Postconcussive Symptoms in OEF/OIF Veterans Presenting to a Polytrauma Clinic with a
History of Traumatic Brain Injury

by

George J. Zeckler

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Postconcussive Symptoms in OEF/OIF Veterans Presenting to a Polytrauma Clinic with a History of Traumatic Brain Injury

Background

Introduction

Since October 2001, approximately 1.80 million U.S. service members have been deployed in support of Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF; (Tanielian & Jaycox, 2008). The principal “battlefields” for these operations are Iraq and Afghanistan, respectively. Service members, referred to as soldiers or warfighters in the literature, deployed and operating within either of these combat environments are exposed to extended periods of deployment-related stress and traumatic events, both psychological and physical. Psychologically traumatic events that occur during deployment may manifest themselves as symptoms of post-traumatic stress disorder (PTSD), whereas physical injuries during deployment frequently include traumatic brain injuries (TBI). Based on survey results from the RAND Corporation, it is estimated that over 300,000 service members who have returned from OIF and OEF are currently experiencing symptoms of PTSD or Major Depressive Disorder (MDD), and nearly 320,000 may have experienced a mild traumatic brain injury (MTBI) during deployment (Tanielian & Jaycox, 2008).

MTBI is the most common type of physical injury occurring to U.S. military personnel in OIF and OEF (Warden, 2006), with blast injury being the most common cause (Warden, 2006). Accordingly, Gaylord et al. (2008) report that explosive devices account for 43 to 50% of all injuries in current day conflicts, and over 60% of blast injuries result in TBI. A similar review of studies of head injuries found that between

79% and 88% of injuries seen within a combat field setting were due to explosions (Hoge, et al., 2008; MacGregor, et al., 2009). Studies of Army combat brigades returning from combat deployment have shown prevalence rates of MTBI (as a percentage of all injuries), ranging from 18% to as high as 22.8% (Hoge, et al., 2008; Terrio, et al., 2009). The high prevalence rates for MTBI and PTSD occurring within the U.S. military's combat Veteran population have resulted in these injuries being labeled as the "signature injuries" of the wars in Iraq and Afghanistan (Hoge, et al., 2008). The high rates of TBI within the military make it imperative that providers across health care disciplines can recognize symptoms associated with TBI and understand important factors related to these symptoms. The present exploratory study will attempt to identify a broad set of clinical factors that may impact expression of postconcussive symptoms, with the expectation that these factors will be important for providers to consider in the process of TBI assessment within this Veteran population.

Mild Traumatic Brain Injury (MTBI)

MTBI criteria.

An estimated 1.5 million brain injuries occur annually in the United States, with more than five million Americans living with impairment resulting from traumatic brain injury (TBI) and an estimated annual rate for TBI of 220 cases per 100,000 people (Kraus & Sorenson, 2000). In the civilian population, the most common mechanisms of TBI are motor vehicle accidents, falls, and assaults (Langlois, Rutland-Brown, & Wald, 2006). Relative to civilians, military personnel may encounter unique risks within the combat environment that can lead to one or more MTBIs over a period of time, including MTBIs that may not be immediately recognized (Kennedy, et al., 2007). Risk factors for TBI

within the military include being significantly younger, lower in rank, and male (Hoge, et al., 2008).

TBI may result from blunt trauma to the head, rapid acceleration or deceleration of the head, and/or explosive blast forces (National Center for Injury Prevention and Control, 2003). TBI is typically diagnosed when, as a result of head injury, any period of observed or self-reported temporary confusion, disorientation, impairment or loss of consciousness; or any period of observed or self-reported dysfunction of memory (amnesia) occurs proximate to the time of injury (National Center for Injury Prevention and Control, 2003). These forces can be delivered on a continuum from none to very severe, and the severity of brain injury is associated with the severity of this force (Kibby & Long, 1996).

About 80% of all TBIs are ‘mild’ (MTBI), also known as ‘concussions’ (Broomhall, et al., 2009). Currently, there is no definite consensus on the clinical criteria used to define MTBI; however, most diagnostic criteria define MTBI as an alteration of consciousness (AOC) or a loss of consciousness (LOC) of up to 30 minutes (Stein & McAllister, 2009), as well as a Glasgow Coma Scale (GCS) score of 13 to 15 at 30 minutes post-injury (Broomhall, et al., 2009). The Glasgow Coma Scale is a tool used by clinicians as an index of injury severity, to describe level of consciousness, and to assess and grade brain dysfunction severity and outcome in patients with TBI (Jennett & Bond, 1975; Teasdale & Jennett, 1974). MTBI may also include posttraumatic amnesia (PTA; loss of memory of events prior to or following the MTBI) of less than 24 hours in duration. Length of PTA is considered a marker for the degree of TBI severity and a sensitive predictor of recovery (Klein, Caspi, & Gil, 2003). Severe TBI is defined by a

GCS score of between 3 and 8, LOC of more than 6 hours and/or PTA of more than 24 hours (Joseph & Masterson, 1999; Levin, Gary, et al., 1987; Williams, Evans, Needham, & Wilson, 2002). Those falling in between the defined AOC/LOC, PTA, and GCS criteria for mild and severe TBI are considered ‘moderate’ TBIs (Joseph & Masterson, 1999).

No screening instrument can reliably make a diagnosis of TBI. Moreover, TBI severity cannot be reliably determined by presentation of current post-concussive symptoms on screening instruments, as post-concussive symptoms are not necessarily specific to concussion (Garden & Sullivan, 2010; Iverson, 2006; Iverson & Lange, 2003). The gold standard remains an interview by a skilled clinician (Summerall, 2008). When available, thorough assessments include observer reports, acute neurological status, and neuroimaging. Therefore, in assessing symptoms associated with TBI, health care providers may consider various factors associated with the features of the individual injury, severity of the injury, and the time interval from injury to assessment that may influence the level of functional and cognitive achievement (Stein & McAllister, 2009).

Post-concussive symptoms (PCSx).

In the acute phase after MTBI, individuals commonly report post-concussive symptoms (PCSx) such as headache, fatigue, irritability, sensitivity to light, dizziness, and a variety of emotional, psychosocial, and cognitive difficulties (Joseph & Masterson, 1999). Most individuals have an alleviation of PCSx over the subsequent days to weeks following injury, typically 4 to 12 weeks (Uzzell, 1999). Although the majority of MTBIs fully recover within 3-6 months, between 10-15% of those with a MTBI will experience chronic and persistent postconcussive symptoms for a year or more after

injury (McAllister & Arciniegas, 2002). The maintenance of persistent neuropsychiatric symptoms can meet criteria for diagnosis of “postconcussive syndrome” (PCS; American Psychiatric Association, 2000).

Because conclusive anatomic changes to the brain may not be visible in neuroimaging following MTBI (Luis, Vanderploeg, & Curtiss, 2003), self-reported symptoms are commonly assessed in an attempt to evaluate and characterize the patient’s condition. These common PCSx can be classified and analyzed in terms of separable somatic, cognitive, and affective symptom clusters (Caplan, et al., 2010; Cicerone & Kalmar, 1995; Levin, Mattis, et al., 1987). Although PCSx can be conceptualized as separable clusters of symptoms, the PCSx clusters maintain relatively strong interrelations between them as well (Potter, Leigh, Wade, & Fleminger, 2006). However, when comparing clusters of PCSx among samples of injured and non-injured controls, the findings suggest the individual PCSx clusters are stable across a range of different populations, sampling methods, and instruments (Bohnen, Wijnen, Twijnstra, van Zutphen, & Jolles, 1995; Ettenhofer & Barry, 2012). Therefore, examination of PCSx clusters—rather than solely individual or total symptoms—may provide clinicians with a base from which to target specific symptoms more closely for more thorough assessment and rehabilitation planning (Caplan, et al., 2010).

Post-Concussive Symptoms Following TBI

Somatic symptoms.

Physical or somatic complaints following MTBI include fatigue, disordered sleep, sensitivity to bright light, balance problems, dizziness, double vision, seizures, and frequent or severe headaches (Kennedy, et al., 2007; Vanderploeg, Curtiss, & Belanger,

2005). TBI is frequently associated with pain at time of injury as well as chronic pain over time, such as neuropathic and/or central pain (Formisano, Bivona, Catani, D'Ippolito, & Buzzi, 2009; Iverson & McCracken, 1997). Similarly, headaches are frequently experienced following a TBI. In Hoge et al.'s (2008) analysis of physical health outcomes corresponding with LOC in a military Veteran sample, only headache continued to be significantly related to MTBI after adjusting for PTSD and depression. The literature provides evidence indicating a neurologic role in both the development and maintenance of detrimental TBI outcomes. A study by Ruff, Ruff, and Wang (2008) of 126 OEF/OIF Veterans with MTBI found that Veterans with neurological deficits had indeed been subjected to more explosions and were more likely to have headache, features of migraine, more severe pain, increased prevalence of headaches, PTSD, and diminished sleep with nightmares. Relative to severity level of TBI, the number of TBI patients with post-traumatic headache at one year follow up has been found to be lower in those with longer coma duration and more severe TBI (Formisano, et al., 2009).

Psychiatric symptoms.

TBI PCSx can also include psychiatric symptoms such as irritability and being short-tempered, impulsivity, anxiety concerning dreams, aggressive and angry behavior, sadness and depression, and more rarely, mania or psychosis (French & Parkinson, 2008). Severely head-injured patients are often unable to work, live independently, support themselves, or participate in several previous activities, contributing to changes in self-concept and beliefs about the self and about the future (Miller, 1993). However, the most common post-TBI anxiety symptoms include generalized anxiety, fearfulness, intense worry, social withdrawal, interpersonal sensitivity, and disturbed conduct (Rao &

Lyketsos, 2002; 2003). Affective PCSx have considerable overlap with typical PTSD symptoms and demonstrate potential problems with measuring or controlling for PTSD incidence rates in those persons with MTBI (Rao & Lyketsos, 2002). These symptoms are fundamental to recognizing for treatment while distinguishing them as consequences of the challenging adjustment to TBI, other physical disabilities, cognitive limitations, posttraumatic memories, and other psychological difficulties (Kennedy, et al., 2007). The present study will examine results of self-report psychiatric measures in order to provide preliminary evidence for their role in facilitating appropriate interpretation of PCSx.

Cognitive symptoms and deficits.

The literature describes that common cognitive difficulties following TBI may include self-reported problems in working and short-term memory, attention and concentration, problem-solving and general intellectual skills, and language comprehension and production (Bohnen, Jolles, & Twijnstra, 1992; Cicerone & Azulay, 2002; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006; Parker, 2002; Ruff, Evans, & Marshall, 1986). Objective cognitive deficits can include impairments in attention, information-processing speed, motor skills, memory, verbal learning, and executive functions such as reasoning, planning, judgment, self-awareness, and abstraction (Dikmen, et al., 2009; Heitger, et al., 2006; Hickling, Gillen, Blanchard, Buckley, & Taylor, 1998; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009; Nelson, et al., 2011; Rassovsky, et al., 2006). These deficits may also include a reduction in motivation levels and the capabilities to initiate behaviors and/or self-monitor (Dikmen, McLean, & Temkin, 1986). Deficits in executive functions affect the ability to integrate and have

insight into the events surrounding the injury (Lux, 2007). In MTBI, long-term persistent attention and memory difficulties may go unnoticed on standard neuropsychological tests, despite complaints by MTBI patients (Ozen & Fernandes, 2011). In MTBI, cognitive deficits normally resolve over time, with near-complete resolution by three to six months post injury or earlier (Dikmen, et al., 1986; Frencham, Fox, & Maybery, 2005; Heitger, et al., 2006).

In a study of 53 OEF/OIF Veterans with MTBI measuring the influence of MTBI on neuropsychological functioning in the post-acute phase, Nelson et al.'s (2009) results demonstrated significant effects for memory, attention, and executive functioning. Additionally, Rassovsky et al. (2006) measured verbal memory and speed of information processing on functional outcome one year following MTBI. They found that information-processing speed significantly mediated the association between the MTBI and post-TBI cognitive functioning. Likewise, Hickling, Gillen, Blanchard, Buckley, & Taylor, (1998) administered neuropsychological testing to those with motor vehicle accident (MVA) TBIs, showing that subjects who had LOC during their MVA had increased impairment levels on speed dependent tests and delayed recall of verbal information. Furthermore, in a meta-analysis of TBI research measuring neuropsychological domains, the most prominent, significant effect sizes were demonstrated in attention ($g = .25, p < .01$) and processing speed ($g = .47, p < .001$) measures in the post-acute phase of MTBI (Frencham, et al., 2005).

By contrast, studies of cognitive outcomes for patients with moderate to severe TBI have identified significant, long-term cognitive deficits and functional limitations which can persist for several years post injury (Dikmen, et al., 2009; Dikmen, Machamer,

Powell, & Temkin, 2003). Lannoo et al. (1998) found moderate to severe TBI patients scored significantly worse than controls on measures of attention, memory and learning, information processing, reaction time, verbal fluency, and mental flexibility. Similarly, Tate, Feneleon, Manning, and Hunter's (1991) evaluation of severe TBI patients found deficits in learning and memory, as well as slowed information processing, to be the most common neurocognitive deficits. For patients with moderate to severe TBI, deficits in cognitive performance are greater and persist over time, compared with MTBI patients and controls (Dikmen, Temkin, McLean, Wyler, & Machamer, 1987; Dikmen, Machamer, Winn, & Temkin, 1995), including significant impairments in learning and retention (Zec, et al., 2001). Even at one year post injury, significant differences between TBI patients and controls have been demonstrated on neuropsychological tasks measuring memory, processing speed, and problem solving (Dikmen, et al., 1995). The present study will evaluate whether post-concussive symptoms are related to objective neuropsychological assessment data in a sample of OEF/OIF veterans with a history of TBI.

TBI Comorbidity with Psychiatric Disorders

Readjustment from TBI may be strongly related to pre-injury factors, such as emotional adjustment and psychiatric history (Dikmen, Temkin, & Armsden, 1989; Karzmark, Hall, & Englander, 1995; Lishman, 1988), and post-injury factors, such as psychiatric symptoms (Bryant & Harvey, 1999; Dikmen, et al., 1986; Landre, et al., 2006) and stress (Machulda, Bergquist, Ito, & Chew, 1998). For example, those with diagnosis of a psychiatric disorder prior to MTBI may be four times more likely to persistent PCSx than those without prior psychiatric history (Luis, et al., 2003). Similarly,

McAllister and Arciniegas' (2002) review of TBI literature related to psychiatric complications following TBI concluded that psychiatric diagnoses such as depression and PTSD are predictive of persistent PCSx. As a result of this comorbidity, some have speculated as to whether persistent PCSx are better attributed to the remote MTBI with failure to improve, to comorbid conditions such as PTSD and depression, or a combination of these factors (Stein & McAllister, 2009). Because psychological factors appear to play a role in the ongoing perpetuation of symptoms (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009), early intervention following MTBI is considered advantageous to achieve resolution of PCSx (Mittenberg, Canyock, Condit, & Patton, 2001).

It has been suggested that multiple combat deployments increase the risk of trauma and the exacerbation of TBI PCSx and PTSD symptoms (Stein & McAllister, 2009). Therefore, survivors of TBI may be at risk for poor psychological adjustment following injury and can be considered a high-risk group for developing severe, long-term psychiatric disorders (Broomhall, et al., 2009), such as major depressive disorder (MDD), general anxiety disorder (GAD), and PTSD (Hiott & Labbate, 2002). Although the specific etiology continues to be unclear, psychiatric syndromes are persistently present at an elevated rate following TBI (Rogers & Read, 2007), and are predictive of persistent PCSx (McAllister & Arciniegas, 2002). One study of mild-to-severe TBI patients found the following rates of comorbid psychiatric disorders: 17% had PTSD, 48% had MDD, 14% had Obsessive-Compulsive Disorder (OCD), and 11% had Panic Disorder (Golding, Bass, Percy, & Goldberg, 2009). Similarly, Hibbard, Uysal, Kepler, Bogdany, and Silver (1998) found that TBI was a risk factor for consequent psychiatric

disabilities. Following TBI, the most common Axis I diagnoses were MDD and anxiety disorders, such as PTSD, OCD, and panic disorder, including 44% of individuals presenting with two or more Axis I diagnoses following TBI.

Because the event surrounding the TBI may have been a psychologically traumatic event, PTSD symptoms may occur following TBI. The literature addressing the issue of comorbidity between PTSD and TBI, a combination of civilian and combat Veteran studies, provides a wide range of estimates of the prevalence rates of PTSD following TBI, ranging from 0-56% (McMillan, 2001). One study of severe TBI survivors found a prevalence rate of 18% for moderate-to-severe PTSD symptoms (Williams, et al., 2002). In a similar study by Bryant, et al. (2000) of severe TBI patients after injury, PTSD was diagnosed in 27% of patients.

In Veterans, a diagnosis of PTSD following combat-related MTBI has been shown to be significantly correlated with persistent post-concussive symptoms (Schneiderman, Braver, & Kang, 2008). Potentially, cognitive impairment and emotional control problems associated with MTBI may be detrimental to the warfighter's psychological resilience that is required to overcome psychiatric comorbidities that could occur subsequent to the MTBI, such as PTSD and depression (Lew, et al., 2008). Recent studies of military populations are demonstrating evidence of increased incidence rates of PTSD in groups with TBI compared to groups without a TBI (King, 2008). Gaylord et al. (2008) measured incidence rates of PTSD and MTBI in a sample of OEF/OIF Veterans and found the following incidence rates: PTSD, 32%; MTBI, 41%; and 18% of the sample had concurrent diagnoses. Similarly, in a study of an OIF Veteran sample, Hoge et al. (2008) found that 44% of those who reported LOC (a key feature associated

with MTBI) met criteria for PTSD, as well as 27% who reported an altered mental status, 16% with other injuries, and a 9% rate for those who had not suffered an injury. Additionally, a survey of OEF/OIF Veterans by the RAND Corporation reported a rate of 18.5% soldiers returning with PTSD or depression and 19.5% reporting probable MTBI. Of those who experienced a TBI, over 1/3 of respondents reported overlapping symptoms of MTBI and PTSD (Tanielian & Jaycox, 2008). However, the Hoge et al. (2008) and RAND Corporation significant prevalence rates (Tanielian & Jaycox, 2008) may be elevated due to their usage of self-report from non-clinical samples. To further explore the relationship between PTSD and MTBI within a clinical sample, the present study will evaluate differences in reported PCSx severity based on presence or absence of a diagnosis of PTSD as well as explore the relationship between PCSx severity and PTSD symptom reporting.

As a result of psychiatric comorbidity, some have speculated as to whether persistent PCSx are better attributed to the remote MTBI with failure to improve, to comorbid conditions such as PTSD and depression, or a combination of these factors (Stein & McAllister, 2009). Because psychological factors appear to play a role in the ongoing perpetuation of symptoms (Belanger, et al., 2009), thorough assessment of psychiatric symptoms in addition to post-concussive symptoms is necessary for determining the extent of clinical symptoms following TBI. Because post-concussive measures such as the Neurobehavioral Symptom Inventory (Cicerone & Kalmar, 1995) are not designed to measure psychiatric symptoms per se, validated psychiatric self-report measures are often used along with the NSI when assessing patients with a history of TBI.

Symptom Overlap

From a diagnostic and treatment standpoint, many PCSx symptoms commonly experienced after MTBI overlap with symptoms of other disorders, including PTSD (Hoge, et al., 2008). Some overlapping psychological symptoms of MTBI and PTSD include depression, anxiety, sleep disruption, fatigue, irritability/anger, hyperarousal, and avoidance (Stein & McAllister, 2009). Additionally, MTBI and PTSD share overlapping cognitive symptoms of impaired learning and forgetfulness, slowed thinking and decreased processing speed, difficulty concentrating and becoming overwhelmed in completing simple tasks, and memory impairment (Kennedy, et al., 2007; Rao & Lyketsos, 2002).

This comorbidity and symptom overlap presents a unique challenge to clinicians in assessing, diagnosing, and differentiating between PCSx and PTSD (Brenner, et al., 2009; Campbell, et al., 2009). Consequently, the role MTBI plays in the development of PTSD and the rate of comorbidity between the two are not absolutely certain. Due to the significant numbers of service members experiencing symptoms of either or both MTBI and PTSD as a result of OEF and OIF combat deployments, the issue of the relationship between MTBI and combat-related PTSD, including risk factors and associated sequelae, must be better understood in order to improve the assessment and treatment of MTBI and PTSD symptoms.

Factors Related to Persistent PCSx.

An increasing proportion of Veterans of the OEF and OIF conflicts have seen multiple incidents of wounding and death and have been exposed to multiple explosive munitions that may be capable of producing TBI, either through the shock waves

themselves or from the blunt force to the head by an object following the blast (DePalma, Burris, Champion, & Hodgson, 2005; Taber, Warden, & Hurley, 2006). Previous studies of Veterans with TBI that suggest the occurrence of multiple TBIs is associated with higher levels of PCSx as well as more persistent levels of PCSx (Guskiewicz, et al., 2003; Hoge, et al., 2008; Kennedy, et al., 2007). In Hoge et al.'s (2008) comparison of soldiers with MTBI and those with other injuries, soldiers who reported MTBI were significantly more likely to report high combat exposure and intensity, a blast mechanism of injury, more than one exposure to a blast or explosion, and being hospitalized during deployment. Individuals who experience multiple MTBIs often require extended recovery time periods (Guskiewicz, et al., 2003). The lack of "down-time" for warfighters in combat settings has been suggested to increase the risk for soldiers who have had multiple MTBIs to develop persistent PCSx (Hoge, et al., 2008). The concurrent emotional toll of the combat environment and physical injuries occurring in addition to the MTBI, typically emerging from blast exposure, complicates the clinical presentations and assessment in this population of combat Veterans with MTBI (French & Parkinson, 2008).

The profoundly stressful and hazardous context in which these injuries are endured sets them apart in compelling ways from the majority of brain injuries seen in civilian settings. Different from civilian TBIs, the effects of TBIs occurring within the combat environment are influenced by at least four variables operating within the combat environment that lead to an increased risk for persistent PCSx: the physically and emotionally traumatic conditions in which many concussions occur, the high incidence of comorbid psychological conditions following MTBI, the potentially repetitive and

collective nature of concussions sustained over a combat deployment, and the difficulty in adhering to typical suggestions for postconcussive care, such as rest (Lew, et al., 2008). These mechanisms could partially explain why military TBI patients report relatively high levels of psychological symptoms and PCSx following TBI (Broomhall, et al., 2009). Furthermore, soldiers with MTBI report significantly higher rates of physical and mental health difficulties than soldiers with other injuries (Lew, et al., 2008). Hoge et al. (2008) found that injuries with LOC were associated with a much greater risk of health problems than injuries with only altered mental status. A study by Luis, Vanderploeg, and Curtiss (2003) comparing over 250 male combat Veterans with MTBI to groups of uninjured controls reported that the most prominent predictors of persistent PCSx were early life psychiatric problems, such as anxiety or depression, inadequate social support, lower intelligence, and interactions between these factors. The findings yield support for the assertion that presence or absence of persistent PCSx is mediated partially by individual resilience, pre-existing psychological status, and psychosocial support (Luis, et al., 2003).

Medication consumption and PCSx.

Prescription medication is a common therapeutic option for management of post-concussive symptoms, ranging from a short-period following TBI to several years following TBI (Meehan, 2011). Following TBI, medication for somatic symptoms, such as sleep disturbance and post-traumatic headache, are common, as well as medications for emotional, psychiatric and cognitive PCSx (Elkind, 1989; Meehan, 2011). In a retrospective review of patients with a history of moderate or severe TBI, the prevalence of current prescription medication use several years (up to 24 years) following injury was

58.9%, with an average number of prescribed medications of 2.64 ($SD = 2.14$; (Yasseen, Colantonio, & Ratcliff, 2008). The most prescribed medication types were anti-convulsants (25.8%), followed by anti-depressants (8.2%), painkillers (8.2%) and anti-anxiety medications (5.9%; Yasseen, et al., 2008). The current study explored whether medication prescriptions (i.e., pain, sleep aid, or psychiatric) were related to increased reported severity of PCSx within the sample.

Summary and Study Rationale

Previous TBI and PCSx research have described the various subcomponents of PCSx, including somatic, cognitive and affective clusters of symptoms. Evidence suggests that a number of factors aside from TBI characteristics may be important, but a significant gap in research exists related to the underlying causes of PCSx. Additionally, despite findings that PCSx consist of separable somatic, cognitive, and affective symptom clusters (Caplan, et al., 2010), little research has investigated how individual clinical factors (e.g., military-service related musculoskeletal injuries, self-reported affective symptoms, objective neuropsychological performance, presence of mood or anxiety disorder, and presence of active medication prescriptions) may be differentially related to PCSx subdomains. To more accurately assess, diagnose, and treat Veterans with a history of TBI, more research is needed to investigate clinical correlates of enduring PCSx in Veterans following TBI.

Therefore, the first aim of the present study is to identify specific clinical correlates of PCSx among a sample of OEF/OIF Veterans with a history of TBI. The results of the present exploratory study are expected to inform clinical practice by helping clinicians more accurately assess neurobehavioral symptoms and the potential factors

related to PCSx severity by evaluating other clinical factors and symptoms beyond self-reported postconcussive symptoms on the NSI.

The second aim of the present study is to explore specific injury factors that may be related to PCSx. We expected that multiple TBIs (versus one TBI), greater TBI severity, less time since most recent TBI, and presence of a musculoskeletal injury diagnosis may be associated with higher PCSx.

The third aim of the present study was to evaluate whether presence of a pain, sleep, or psychiatric medication was related to higher levels of PCSx reporting within the sample. The intent of this aim was exploratory in nature, with the expectation that the present study's findings could inform future studies related to the effects of medication consumption on post-concussive symptoms.

The fourth aim was to evaluate the relationship of self-reported cognitive limitations and objective neuropsychological testing data. To evaluate this aim, the present study examined whether levels of overall PCSx reporting were related to objective neuropsychological performance (by cognitive domain) within the sample. Based on previous results within the literature, we expected that poorer neuropsychological performance would be associated with higher levels of PCSx reporting.

The fifth aim was to explore the degree to which psychiatric functioning and overall PCSx were related. To evaluate this aim, the present study examined the degree to which psychiatric symptoms were related to overall PCSx. Consistent with previous findings within the literature, we expected self-reported PTSD symptoms, depressive symptoms, and anxiety symptoms (as measured on psychiatric self-report measures) to be

most related to higher PCSx reporting. Similarly, we expected that presence of a diagnosis of either PTSD, major depressive disorder, or an anxiety disorder would be related to PCSx within the sample.

Methods

Participants

This retrospective medical record review was approved by the institutional review board of the Greater Los Angeles Veterans' Administration Medical Center (VAMC). The medical records review included 96 consecutive patients referred for neuropsychological assessment within the Greater Los Angeles VAMC Polytrauma program between 2006 and 2009. Referral to the Polytrauma program required screening positive for possible TBI by a VA clinician and requesting further evaluation or treatment on the part of the patient. The integrated, multidisciplinary polytrauma team approach was comprised of a neuropsychologist, social worker, physical therapist, physiatrist, occupational therapist, and vision rehabilitation specialist. The following patients were excluded from the analysis: patients who were still on active duty ($n=22$), patients who did not serve in OEF or OIF ($n = 5$), patients who did not have an identifiable history of TBI ($n = 4$), patients who were missing 50% or more of data points ($n = 2$) or patients whose effort was judged to be insufficient ($n = 4$)—based on performance below established cutoffs on measures of effort and/or their overall performance or symptom presentation was considered to be invalid by the evaluating clinician. A total of 61 participants were included in the present analysis.

Procedure

OEF/OIF Veterans referred for neuropsychological assessment to the Greater Los Angeles VA Healthcare System completed a clinical interview, the Neurobehavioral Symptom Inventory (NSI; (Cicerone & Kalmar, 1995), and several other neuropsychological tests and self-report measures (see *Measures* below). Additionally, evaluating providers collected information pertaining to relevant medical history and active prescription medications from patients as well as the VA's electronic medical record, the Computerized Patient Record System (CPRS). The neuropsychological assessment battery, as well as self-report measures administered, differed across patients based on the clinical judgment of the evaluating clinician. The measures included in the present study represent those measures for which sufficient data were available for meaningful analysis and group comparison within the Veteran TBI sample.

Comprehensive neuropsychological assessment reports were generated for each patient following clinical evaluation. The reports included information regarding patient demographics; presenting symptoms (e.g., cognitive complaints, memory complaints, headache, depression and/or anxiety symptoms); medical history (including TBI history); substance abuse and psychiatric history; prescription medication regimen; responses on the NSI, raw scores from neuropsychological assessment measures, and self-report measures administered, and full DSM-IV-TR diagnosis, including Axis V Global Assessment of Functioning (GAF) score. During chart review, each of these variables was systematically coded from the neuropsychological report into a de-identified electronic research record. Patients' demographic characteristics are provided in Table 1.

Head injuries involving alteration or loss of consciousness were considered to be TBIs in the present analysis. Each TBI was coded for severity, based upon the presence

and length of LOC and PTA. TBI severity was coded as “mild without LOC or PTA” for alteration of consciousness but no LOC or PTA; “mild with LOC or PTA” for LOC < 30 minutes and PTA < 24 hours; “moderate” for LOC < 24 hours and/or PTA < 7 days; and “severe” for LOC > 24 hours and/or PTA > 7 days. Previous research suggesting that LOC and PTA are associated with increased post-concussive symptoms and poorer neuropsychological functioning (McCrea, Kelly, Randolph, Cisler, & Berger, 2002; Schneiderman, et al., 2008) was the basis for the distinction between mild TBIs with and without LOC or PTA. Psychiatric diagnostic information was drawn from clinicians’ recorded DSM-IV diagnostic formulation. Presence or absence of active prescriptions for psychiatric, sleep, and pain medications were based upon the target symptoms identified for each medication listed in patients’ electronic medical record.

Measures

Medical characteristics

Several independent variables were created to analyze differences in PCSx within the sample based on these characteristics of interest. Due to a skewed distribution, number of TBIs was recorded as “Multiple TBIs” vs. “Single TBI” to allow comparison of PCSx between these patient subgroups. Additionally, because there were a relatively low number of patients who had either a moderate or a severe TBI, TBI severity was divided into two categories: MTBI and moderate-to-severe TBI combined.

Musculoskeletal injury diagnosis was a variable of interest, with the determining factor for assignment of this variable being that the musculoskeletal injury was military-service related. Medication consumption was coded by whether patients had a prescription for

either a psychiatric, pain, or sleep management medication in their electronic medical record .

Self-report measures.

NSI. The Neurobehavioral Symptom Inventory (NSI; Cicerone & Kalmar, 1995) is a 22-item measure that assesses the post-concussive symptoms as indicated by the ICD-10 (World Health Organization, 1992). This measure looks at several different symptoms across affective, cognitive, and somatic/sensory postconcussive symptom clusters. Responses are selected on a 5-point Likert scale to rate the degree they have been affected by each symptom since the injury. The scale ranges from 0 (*none: rarely if ever present; not a problem at all*) to 4 (*very severe: almost always present and I have been unable to perform at work, school, or home due to this problem; I probably cannot function without help*). The NSI has been found to correlate with the Brief Traumatic Brain Injury Screen ($r = .48, p < .001$; Schwab, et al., 2007).

NSI scores were used as dependent variables for the current study. Total NSI score was used as the measure of “overall PCSx”. Additionally, for all findings of significant relationships between overall PCSx and clinical variables of interest, post-hoc analyses were conducted in which the NSI was broken down into three subscales—somatic/sensory PCSx, cognitive PCSx, and affective PCSx subdomains—to compare the sample on distinct sub-domains of PCSx. Using NSI total score and somatic/sensory, affective, and cognitive sub-scores has been validated in previous studies of U.S. military personnel with and without TBI (Caplan, et al., 2010). The somatic/sensory PCSx sub-domain includes the following NSI symptoms: feeling dizzy, loss of balance, poor coordination/clumsy, headaches, nausea, vision problems/blurring/trouble seeing,

sensitivity to light, hearing difficulty, sensitivity to noise, numbness or tingling on parts of my body, change in taste and/or smell, and loss of appetite or increase appetite. The cognitive PCSx sub-domain includes the following NSI symptoms: poor concentration/can't pay attention/easily distracted, forgetfulness/can't remember things, difficulty making decisions, and slowed thinking/difficulty getting organized/can't finish things. The affective PCSx sub-domain includes the following NSI symptoms: fatigue/loss of energy/getting tired easily, difficulty falling or staying asleep, feeling anxious or tense, feeling depressed or sad, irritability/easily annoyed, and poor frustration tolerance/feeling easily overwhelmed by things.

BDI-II. The Beck Depression Inventory-II (BDI) is a 21-item self-report measure that identifies symptoms of depression that have been experienced over the last 2 weeks. This measure uses a 4-point scale (0-3) and takes 5-10 minutes to complete. The BDI-II is a highly reliable and valid measure with an average coefficient alpha of .91 (Dozois & Covin, 2004), a reliability coefficient of .93 (Beck, Steer, & Brown, 1996), test- retest reliability of .72 (Yin & Fan, 2000) and a convergent validity with the Beck Depression Inventory-I of $r = .93$ (Beck, et al., 1996). The BDI-II has been used in prior research to measure depressive symptoms in head-injured populations (Sawchyn, Brulot, & Strauss, 2000; Suhr & Gunstad, 2002; Trahan, Ross, & Trahan, 2001).

BAI. The Beck Anxiety Inventory (BAI; (Beck, Epstein, Brown, & Steer, 1988) is a reliable and valid 21-item self-report inventory for measuring the severity of anxiety symptoms in psychiatric populations. The measure shows high internal consistency, Chronbach's alpha coefficient of .92, and test-retest reliability over one week of $r = .75$.

The BAI is a useful measure for discriminating between anxious and non-anxious diagnostic groups; however, the BAI has a strong correlation with BDI scores, $r = .48$.

PCL-C. The PTSD Checklist – Civilian (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996) is a 17-item self-reported measure that asks participants to rate the severity level of symptoms they have experienced in the last month as they relate to a stressful life experience. The symptoms on the questionnaire are directly parallel DSM-IV symptoms of re-experiencing, avoidance, and hyperarousal. The PCL-C displays high internal consistency through the Cronbach's alpha coefficient of .94 (Ruggiero, Del Ben, Scotti, & Rabalais, 2003). Ruggiero and colleagues (2003) also found high convergent validity between the PCL-C and the Impact of Event Scale (IES) and Mississippi Scale for PTSD - Civilian ($r > .75$).

Neuropsychological performance.

Neuropsychological score conversion and global cognition. The raw scores from neuropsychological measures were converted into *T*-scores based upon published normative data (see Appendix for specific variables and normative data utilized). Mean *T*-scores for individual cognitive domains were calculated for participants whose available data met the following minimum requirements: 2 of 3 processing speed variables; 3 of 5 executive function variables; 2 of 3 working memory variables; 1 of 2 learning variables; 2 of 4 recall variables, and 2 of 2 motor variables. A Global Cognition *T*-score was then computed based upon the mean domain *T*-score for participants with 5 or more of 7 domain *T*-scores available.

Processing speed. Processing speed is the rate at which mental tasks are carried out when speeded responses are necessary. Slowing of mental activity is evident in delayed

reaction times and in longer than average total performance times when a specific motor disability is not present (Lezak, Howieson, & Loring, 2004b). Processing speed is strongly related to processes of attention and concentration. Impaired attention and concentration are among the most common mental problems associated with brain damage (Leclercq, Deloche, Rousseaux, & Zimmermann, 2002). Furthermore, slowed processing speed can contribute to memory lapses and can occur as a result of brain damage, such as from a TBI. The neuropsychological assessment scores included within the cognitive domain of processing speed within the present study include the Trail Making Test Part A, Digit Symbol Coding, and the Wechsler Adult Intelligence Scale-III (WAIS-III; (Wechsler, 1997a)) Symbol Search subtest.

Executive function. Executive functions encompass a complex collection of processes that are responsible for guiding, directing, and managing cognitive, emotional, and behavioral functions, particularly during active, unfamiliar problem solving (Strauss, Sherman, & Spreen, 2006). The executive functions have four components: volition, planning, purposive action, and effective performance (Lezak, Howieson, & Loring, 2004a). The majority of research suggests that executive processes are part of a system that acts in a supervisory role within the brain-processing structures and includes skills required for purposeful, goal-directed behavior (Lezak, et al., 2004a). Executive functions are measured in TBI assessment, as both TBI and executive deficits are commonly associated with frontal lobe damage. Manifestations of problems with executive function include inappropriate social behavior, problems with decision-making and good judgment, problems with organization, distractibility, and poor planning (Anderson, Bigler, & Blatter, 1995). The neuropsychological assessment scores included

within the cognitive domain of executive function in the present study include: Trail Making Test Part B, Verbal Fluency (FAS), Verbal Fluency (Animals), Ruff Figural Fluency Test, and Wisconsin Card Sorting Test (64 card).

Working memory. Working memory is conceived as either a component of attention or memory within the neuropsychology literature. Attention involves the interaction of cognitive components that allow individuals to filter information based on relevance, hold and manipulate mental representations, and observe and adapt responses to stimuli (Strauss, et al., 2006). Working memory is conceived of as a limited storage capacity for holding information in the short term (from seconds to 1-2 minutes) and for performing mental tasks on the currently retained information (Gazzaniga, Ivry, & Mangum, 2002). Furthermore, working memory includes information that can be acted on and processed, allowing for information to guide behavior when external cues are not present and ensuring that information will be available until it can be encoded into long-term memory (Goldman-Rakic, 1992). Measures of working memory require subjects to hold information in mind while performing a mental task. Furthermore, working memory measures that require subjects to keep track of ongoing mental activity usually involve a minimum amount of short-term memory of what was just done or heard during the performance of another task. Neuroimaging research suggests that the prefrontal cortex, which can be injured during a TBI, is a primary region involved in working memory (Lezak, et al., 2004a). The neuropsychological assessment scores included within the cognitive domain of working memory in the present study include: WAIS-III Digit Span, WAIS-III Arithmetic, and WAIS-III Letter-Number Sequencing.

Learning and recall. Learning and recall are two cognitive domains that involve the processes of acquiring new information, storing or consolidating that information, building on that information, and actively retrieving that information after a delay (Lezak, 2004). The assessment measures used for the cognitive domains of learning and recall in the present analysis (i.e., the CVLT-II, BVMT-R, and Rey-Osterreith Complex Figure—Delayed Recall) include both delayed recall and recognition trials to examine whether a deficiency relates more to the storing of information versus the recall of information (Strauss, et al., 2006). The multiple-trial list-learning tasks of the CVLT-II and BVMT-R measure episodic memory by assessing learning strategies and rate of learning, and by assessing overall level of achievement through short and delayed recall and recognition (Strauss, et al., 2006).

Motor function. Satisfactory motor function is necessary in the performance of nearly all tasks of daily living. Assessments of motor performance typically involve the hands and are useful for identifying motor impairment and making inferences as to the likelihood of lateralized injury to either of the two cerebral hemispheres, as might occur in TBI (Strauss, et al., 2006). To assess motor impairment, the Grooved Pegboard dominant and non-dominant hand measures were included in the calculation of the neurocognitive domain of motor function in the present analysis. The test is a complex coordination task that measures manual dexterity, motor speed, eye-hand coordination, and motivational status (Lezak, et al., 2004b; Strauss, et al., 2006).

Analysis

All analyses were conducted using SPSS 18.0. Descriptive statistics were examined for all variables. Independent-samples *t*-tests were performed to compare

differences in PCSx based on characteristics of interest, including number of TBIs (1 vs. multiple), TBI severity (mild vs. moderate-to-severe), musculoskeletal diagnosis, PTSD diagnosis, mood and/or anxiety diagnosis (other than PTSD), and medication prescription. Binary variables were coded as “0” if the characteristics were absent and coded as “1” if the characteristics were present. Pearson r correlations were used to examine relationships between overall PCSx and continuous clinical correlates of interest, including depressive symptoms, anxiety symptoms, PTSD symptoms severity, and neuropsychological cognitive domains. When correlations between overall PCSx and variables of interest were $p < .05$, post hoc analyses were conducted on the variables of interest examining PCSx by individual subdomain. For this preliminary study, univariate statistics were used instead of multivariate statistics in order to maximize effective statistical power in consideration of sample size limitations.

Results

Patient demographic characteristics are presented in Table 1. The sample was primarily male ($n = 59$, 96.7%) and relatively young ($M = 29.7$), with an average of 12.9 years of education. Branch of service was primarily split between Army ($n = 26$, 44.8%) and Marine Corps ($n = 26$, 44.8%), and conflict deployment was split between OIF ($n = 53$, 86.9%) and OEF ($n = 6$, 9.8%) Table 2 presents the results of independent-samples t tests conducted to examine potential between-group mean differences in NSI scores, represented based on *absence* (coded “0”) or *presence* (coded “1”) of characteristics under study. The table includes *Cohen’s d* effect sizes for each independent-samples t test. Table 3 presents the results of correlation analyses examining the relationship between variables of interest (e.g. psychiatric self-report measures, cognitive domains)

and NSI scores. The results are presented by category: overall NSI score, NSI somatic subscale, NSI cognitive subscale, and NSI affective subscale.

Independent-samples t tests were conducted to examine whether multiple TBIs (versus single TBI) were associated with higher overall PCSx. As presented in Table 2, those with one TBI did not significantly differ in overall NSI score from those with more than one TBI in overall PCSx. Similarly, independent-samples t tests demonstrated that TBI severity was not associated with significantly higher PCSx. Similarly, group differences between patients with MTBI and patients with moderate or severe TBI were non-significant in overall PCSx. Overall, the results indicated that neither number nor severity of TBIs were significantly associated with increased levels of PCSx in this sample.

A Pearson correlation was utilized to determine the strength of relationships between time since most recent TBI and self-reported overall PCSx. Contrary to expectations, greater time since most recent TBI was not significantly associated with self-reported overall PCSx. Using independent-samples t tests to explore the relationship between PCSx and musculoskeletal injuries, higher overall PCSx was observed among Veterans with service-related musculoskeletal injuries within the sample, $t(50) = -2.23$, $p = .03$. Post-hoc analysis to further explore which subscale(s) specifically may have significantly influenced overall PCSx revealed that Veterans with musculoskeletal injuries had significantly higher NSI somatic subscale scores than those without a musculoskeletal injury diagnosis, $t(50) = -2.43$, $p = .02$.

Independent-samples t tests were conducted to explore whether there were significant differences in overall PCSx between patients with and without prescription

medications at the time of assessment. First, the differences in overall PCSx between patients prescribed pain medications approached significance, $t(48) = -1.87, p = .067$, with the patients prescribed pain medications having marginally higher overall mean NSI scores than the patients not prescribed pain medications. Similarly, when performing post analyses by subdomain, independent t test results approached significance between groups in differences in NSI somatic subscale scores $t(48) = -1.97, p = .054$, with patients taking pain medications having marginally higher NSI somatic PCSx than patients not taking pain medications. Second, patients with a psychiatric medication prescription had significantly higher overall PCSx than patients without a psychiatric medication prescription, $t(49) = -4.11, p < .001$. When conducting post-hoc analyses by individual subdomain, the largest effect size was found with the higher affective PCSx subscale scores $t(49) = -4.01, p < .001$. Third, when exploring differences in overall PCSx between patients with and without a prescription for sleep medication, the differences in PCSx were significant, $t(47) = -2.08, p = .04$, with higher NSI scores for patients prescribed a sleep medication. Similar to the presence of a psychiatric medication, post-hoc analysis by subdomain indicated that patients with a sleep medication prescription had significantly higher NSI affective subscale scores than patients without a sleep medication prescription, $t(49) = -2.80, p = .007$.

Pearson correlations were utilized to explore the strength of relationships between objective measures of neuropsychological performance, by individual neuropsychological cognitive domain, and reporting of cognitive PCSx. Analyses revealed that neither global cognition, working memory, processing speed, executive function, visuospatial function, nor motor function was significantly related to self-reported cognitive PCSx. However,

two neuropsychological performance cognitive domains, learning and recall, were related to self-reported cognitive PCSx. Better learning ability was associated with lower levels of self-reported cognitive PCSx, $r = -.284, p = .04$. Additionally, the relationship between recall performance and cognitive PCSx approached significance, $r = -.267, p = .058$.

Pearson correlation analyses were used to examine the relationship between self-reported psychiatric symptoms—depressive symptoms (measured by BDI score, $n = 29$), anxiety symptoms (measured by BAI score, $n = 32$), and severity of PTSD symptoms (measured by PCL-M score, $n = 26$)—and PCSx. Consistent with expectations, correlation analyses confirmed a strong relationship between reported depressive symptoms and overall PCSx, $r = .64, p < .001$, indicating that increased reporting of depressive symptoms was related to increased severity of overall PCSx within the sample. Similarly, self-reported anxiety symptoms were strongly related to overall PCSx, $r = .73, p < .001$, indicating that increased reporting of anxiety symptoms was related to increased severity of overall PCSx. Furthermore, correlation analyses confirmed that PTSD symptom severity and overall PCSx were strongly related, $r = .87, p < .001$. Among the PCSx subdomains analyzed post-hoc, the strongest relationships consistently identified between reported psychiatric symptoms (i.e., depressive, anxiety, and PTSD) and PCSx subdomain was the affective PCSx subdomain.

To further examine psychiatric functioning and its relation to PCSx reporting, independent-samples t -tests examined group differences in PCSx based on presence or absence of a mood or anxiety disorder. Consistent with expectations, patients with a diagnosis of major depressive disorder had significantly higher overall PCSx than

patients without a diagnosis of depression $t(52) = -2.35, p = .02$. However, independent-samples t tests did not demonstrate any significant differences in overall PCSx or either of the PCSx subscales based on presence of an anxiety disorder diagnosis.

Discussion

This retrospective, cross-sectional exploratory study was conducted to identify clinical correlates of PCSx among OEF/OIF Veterans with a history of TBI as a starting point for future large-scale prospective research related to the causes of PCSx. The identification of clinical correlates of PCSx among Veterans with a history of TBI is important to maximizing clinicians' ability to provide early identification and intervention for these symptoms.

This medical chart review of OEF/OIF Veterans with history of TBI demonstrated a wide variety of post-concussive symptoms, psychiatric comorbidity, and affective symptoms within the sample. Findings from this study provide evidence that increased severity of post-concussive symptoms was associated with increased depressive and anxiety symptom reporting, diagnosis of major depressive disorder, severity of PTSD symptoms, musculoskeletal injury diagnosis, and medication treatment for sleep, pain, or psychiatric symptoms. Similarly, higher levels of self-reported cognitive post-concussive symptoms were related to lower levels of objectively-measured learning and recall abilities.

Among all clinical variables examined, psychiatric symptoms were most strongly associated with PCSx reporting. Consistent with previous studies measuring the relationship between PCSx and symptoms of depression and anxiety, (Brenner, et al., 2010; Dischinger, Ryb, Kufera, & Auman, 2009; Lew, et al., 2009; Sawchyn, et al., 2000;

Suhr & Gunstad, 2002; Trahan, et al., 2001) the findings provide evidence that general distress is related to elevated PCSx reporting in these young Veterans presenting for neuropsychological evaluation. Moreover, when PCSx symptoms were further examined by symptom cluster (i.e., somatic, cognitive, and affective subdomains), all three self-report affective measures (i.e., BDI-II, BAI, PCL-M) had strong relationships with the affective PCSx cluster. These findings provides support for examining PCSx by NSI symptom subdomains for increased specificity in assessment and targeting of specific symptoms, along with using psychiatric self-report measures to further inform TBI assessment.

Similarly, the present study's large effect size for PTSD diagnosis ($d = .204$) provides supporting evidence to previous research of OEF/OIF Veterans which had found PTSD to be the strongest factor associated with severity of PCSx (Schneiderman, et al., 2008). In a similar study using the NSI as a measure of PCSx in OEF/OIF Veterans in a VA Medical Center, PTSD symptoms accounted for a majority of the variance in individual PCSx (Benge, Pastorek, & Thornton, 2009). The strong relationship between PCSx and PTSD symptoms as observed in this study and previous studies (Brenner, et al., 2010; Hoge, et al., 2008; Lew, et al., 2009; Schneiderman, et al., 2008) underscore the importance of evaluating PTSD symptoms, in conjunction with PCSx, in Veterans with a history of TBI. One limitation to consider related to the affective self-report measures (i.e., BDI-II, BAI, PCL-M) used in the present analysis is that the measures share a number of diagnostic symptoms with our measure of post-concussive symptoms (e.g., anxiety, depression, irritability), the NSI. This shared variance resulting from the overlapping symptoms may have elevated relationships between these constructs.

Additionally, a limitation with the available self-report measure data is the relatively large amount of missing data for three affective self-report measures (i.e., BDI-II, BAI, PCL-M), reducing the ability for within and between patient comparisons within this chart-review study. Therefore, future studies systematically examining the relationship among affective symptoms, and PCSx among samples of OEF/OIF Veterans with history of TBI will be needed in order to replicate and extend the current findings.

The present analysis also confirms previous empirical evidence that self-reported post-concussive symptoms are associated with level of cognitive impairment (Bohnen, et al., 1992; Cicerone & Azulay, 2002; Heitger, et al., 2009). Specifically, learning ($p = .04$) and recall ($p = .058$) were significantly related to self-reported cognitive PCSx. Additionally, among five of the six neurocognitive performance domains examined, the pattern of data demonstrated a trend of lower objective performance being related to increased levels of post-concussive symptoms. Although the relationships between performance and post-concussive symptoms reporting related to the other cognitive domains were not statistically significant, the observed trends suggest that lower overall cognitive performance is related to higher levels of PCSx reporting. Potentially, learning and recall deficits are more easily recognized by patients following TBI than other potential cognitive deficits. Previous research has found that self-reported cognitive limitations in memory and concentration, such as problems with learning and recall, are commonly reported by patients following TBI and are strongly related to objective findings measuring these areas of cognitive ability (Cicerone, Mott, Azulay, & Friel, 2004; Corrigan, Bogner, Mysiw, Clinchot, & Fugate, 2001; Hanks, Rapport, Millis, & Deshpande, 1999). In addition to the potential effects of cognitive decline on affective

symptoms, the present study's results do suggest a relationship between higher self-reported cognitive limitations and decreased cognitive performance.

The lack of significant correlations among PCSx and the majority of cognitive domains (i.e., executive function, working memory, visuospatial processing, processing speed, motor function) is consistent with previous findings showing a lack of relationship between subjective and objective cognitive performance in patients with a history of TBI (Landre, et al., 2006). In sum, the current pattern of results is best interpreted as supporting evidence that some indicators of cognitive ability may be related to self-reported cognitive PCSx, particularly learning and recall. Although the present study measured the relationship between self-reported cognitive limitations and objective neuropsychological performance in a Veteran sample with history of TBI, prospective studies that systematically measure both self-reported and objective cognitive abilities among samples of Veteran TBI patients and controls might also provide enhanced ability to identify the causes of different forms of PCSx, including cognitive PCSx.

The significant differences in overall PCSx between TBI patients with and without a musculoskeletal injury diagnosis within the sample is consistent with studies of OEF/OIF Veterans demonstrating that physical injuries and chronic pain also have higher levels of PCSx (Lew, et al., 2009). Furthermore, somatic PCSx was the only PCSx subdomain with significant differences between mean scores of TBI patients with and without a musculoskeletal injury diagnosis, suggesting that this significant difference in somatic PCSx scores was a driving factor contributing to the significant differences in overall PCSx between the two groups.

The present study can be distinguished from several previous studies of TBI in Veteran samples in that the present study examined the specific somatic, cognitive, and affective PCSx subdomains. These exploratory results demonstrate the utility of parsing out the PCSx subdomains to more specifically assess the types of PCSx most significantly impacting individuals with TBI. This degree of specificity of evaluation may facilitate more targeted rehabilitation and treatment planning. Future TBI research examining PCSx by symptom subdomain might provide additional data regarding specific clinical correlates of self-reported PCSx within samples of Veterans with a history of TBI.

With regard to medication prescriptions within the sample, the most prominent differences in overall PCSx and each individual PCSx subdomain were found between those patients with and without a psychiatric medication prescription. Interpretation of this result is complicated by the cross-sectional nature of the study. Potentially, patients' reports of higher levels of PCSx (and related psychiatric symptoms) may have warranted a greater need for a psychiatric medication prescription than patients who reported fewer PCSx. Similarly, this study's unique analysis by PCSx subdomains provides insight as to potential explanations for receiving a sleep aid prescription. The fact that the only PCSx subdomain significantly associated with the presence of a prescription sleep aid was affective PCSx suggests that the affective PCSx were the driving factors leading to an overall significant difference between groups of patients with and without a prescription for a sleep aid. By evaluating PCSx by subdomain, clinicians may be able to more effectively determine the appropriate treatments to target the specific PCSx patients are reporting versus providing a standard medication regimen for general PCSx.

The present study did not evaluate prescription medication adherence within the sample. However, poor medication adherence may have played a role in the reporting of higher PCSx among the sample with psychiatric prescriptions. In a study of medication adherence among Veterans with TBI, psychiatric medications (e.g., SSRIs and other antidepressants) were associated with the lowest adherence rates among prescribed medications with the sample (Huggins, et al., 2010) . Therefore, if medication adherence was low within this sample as well, the medications might not have the capability of reducing the symptoms the medications were prescribed for. On the other hand, many psychotropic and other medications used to treat TBI PCSx can themselves be associated with impaired cognitive effects, such as cognitive slowing and problems with memory and attention (McAllister, 2009). Consequently, medication adherence might actually increase certain self-reported PCSx if the individual taking these medications perceives the medication side effects as impairing his/her functioning. Finally, the self-reported PCSx may have been higher within the sample prescribed psychotropic, sleep, and/or pain medications simply based on a lack of effectiveness of the patients' current prescribed pharmacologic treatment regimen (Donaldson, Hoffer, Balough, & Gottshall, 2010; Meehan, 2011).

As a cross-sectional, retrospective design, the present analysis could not evaluate whether having a medication prescription and adhering to the treatment regimen was associated with a change in self-reported PCSx. Future research using a longitudinal design to assess medication adherence among Veterans with a history of TBI could more accurately evaluate whether medication adherence is associated with self-reported PCSx. Additionally, by measuring PCSx along different time points along the medication

treatment continuum, assessment of the changes in self-reported PCSx related to prescription medication adherence could provide further evidence as to the perceived efficacy of medication treatment following TBI.

Previous studies of Veterans with TBI suggest the occurrence of multiple TBIs is associated with higher levels of PCSx as well as more persistent levels of PCSx (Guskiewicz, et al., 2003; Hoge, et al., 2008; Kennedy, et al., 2007). However, several injury factors (i.e., number of TBIs, TBI severity, and time since injury) were not found to be significantly related to differences in PCSx severity within our sample. Although TBI research is comprised of conflicting data regarding the association between TBI severity and levels of self-reported PCSx, the study expected to find significant mean differences in PCSx between patients with mild TBI versus patients with moderate or severe TBI. These non-significant findings may be related to the relatively small sample size of moderate and severe TBI patients within the sample overall, as well as relative to the restricted number of MTBIs overall, limiting the statistical power to detect actual PCSx mean differences between the different levels of TBI severity.

One limitation of the study that should be noted with respect to the results concerns the large number of univariate statistical analyses performed in the present study, which would be expected to increase the likelihood of Type I error. Primarily, missing data prevented the use of multivariate statistical techniques that would have minimized the number of analyses performed. As a result, individual *t*-tests were used to measure each independent dichotomous variable of interest with varying sample sizes. Additionally, multiple correlations were conducted on each continuous variable of interest. However, to account for and minimize Type I error, post-hoc analyses of PCSx

subdomains were only performed when significant correlations were found for overall PCSx, in order to minimize the number of analyses performed to the greatest extent possible while examining hypothesized relationships. The consistency of results found in the majority of analyses performed also provides support that the relationships found were not merely due to chance. Moreover, by determining the majority of expected relationships prior to conducting the statistical analyses, we could have more confidence in the significant findings. However, we caution against over-interpretation of group differences or relationships with marginal significance.

The results suggest that among treatment-seeking OEF/OIF Veterans with a history of TBI and relatively young age, PCSx are more strongly related to psychiatric symptoms and a number of other factors that can occur independently of TBI. Along with assessment of neurobehavioral symptoms, clinicians should evaluate psychiatric symptoms and other potential causes of PCSx when treating patients with history of TBI. However, differences in self-reported PCSx by number or severity of TBIs have not been clearly demonstrated. Therefore, to optimize care to patients with TBI, thorough assessment of the effects of TBI should include examination of other clinical factors that may impact post-concussive symptoms. Accordingly, the study provides solid rationale for clinical practitioners evaluating Veterans with history of TBI to not rely on measures of post-concussive symptoms as the primary measure for determining extent or effects of neural injury, or as the stand alone measure of clinical status after TBI. However, the NSI can be effectively used to inform clinical judgment related to the severity of PCSx and as a basis for identifying specific symptom clusters that may be most relevant to treatment and rehabilitation. Further research is needed to provide an increased

understanding of the influence of psychological and other factors in the maintenance of persistent PCSx among Veterans with a history of TBI.

Table 1. *Patient Demographic Characteristics*

Characteristic	Valid <i>N</i>	<i>n</i> (Valid %)	M (SD)
<i>N</i>	61		
Men	61	59 (96.7%)	
Age in Years	61		29.7 (8.3)
Married	60	17 (28.3%)	
Ethnicity/Race	59		
Hispanic or Latino/a		15 (25.4%)	
Caucasian/White		29 (49.2%)	
African American/Black		6 (10.2%)	
Asian/Pacific Islander		6 (10.2%)	
Other		3 (5.1%)	
Branch of Service	58		
Army		26 (44.8%)	
Marine Corps		26 (44.8%)	
Navy		2 (3.4%)	
Air Force		3 (5.2%)	
Veteran Status	61		
OEF		6 (9.8%)	
OIF		53 (86.9%)	

OEF/OIF	2 (3.3%)
Education in Years	61
	12.9 (1.6)

Table 2. *NSI Score by Psychiatric Diagnoses, Injury Characteristics, and Medication**Regimen*

	Total Valid <i>N</i>	Absent M (SD) <i>n</i>	Present M (SD) <i>n</i>	<i>t</i> ^a	<i>p</i>	<i>Cohen's</i> <i>d</i>
OVERALL NSI SCORE						
Current Mood Disorder Diagnosis ¹	54	37.06 (18.02) 34	48.15 (14.32) 20	-2.35	.02	-.68
Current PTSD Diagnosis	54	13.67 (15.81) 6	44.60 (14.45) 48	-4.90	<.001	-2.04
Current Anxiety Disorder Diagnosis ²	54	41.10 (16.96) 51	42.33 (29.84) 3	-.12	.91	-.05
Musculoskeletal Diagnosis ³	52	35.16 (18.60) 19	45.58 (14.70) 33	-2.23	.03	-.62
Multiple TBI ⁴	55	41.00 (17.74) 38	42.00 (16.90) 17	-.20	.85	-.06
TBI Mild vs. Moderate Severity ⁵	55	41.79 (17.38) 43	39.58 (17.82) 12	.39	.70	.13
Pain medications	50	36.40 (19.36) 20	45.23 (14.03) 30	-1.87	.07	-.52
Sleep medications	49	37.87 (16.68) 30	47.84 (15.87) 19	-2.08	.04	-.61
Psychiatric medications	51	30.48 (15.68) 19	47.84 (13.93) 32	-4.11	<.001	-1.17

Note. ¹ Major Depressive Disorder; ² Other than PTSD; ³ Military-service related; ⁴

Absent = ≤ 1 ; Present = ≥ 2 ; ⁵ Mild = No TBI & MTBI; Moderate = Moderate or Severe TBI.

^a *t* value of independent-samples *t*-test.

Table 3. *Intercorrelations of NSI, Self-Report, and Neuropsychological Domains*

	Valid N	NSI Total	NSI Somatic	NSI Cognitive	NSI Affective
BDI-II	29	.64**	.49**	.63**	.68**
BAI	32	.73**	.66**	.51**	.71**
PCL-M	26	.87**	.67**	.74**	.81**
Time Since most recent TBI	45	.05	--	--	--
Education	55	-.11	--	--	--
Global Cognition	49	-.18	--	--	--
Working Memory	51	-.11	--	--	--
Processing Speed	51	-.21	--	--	--
Executive Functions	46	.07	--	--	--
Learning	52	-.27 ^a	-.23	-.28*	-.21
Recall	51	-.28*	-.20	-.27 ^a	-.29*
Motor Speed	49	-.14	--	--	--

Note. * $p < .05$. ** $p < .01$. ^ p approaching significance at $p = .05$. BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; PCL-M = PTSD Checklist-Military.

Appendix

Neuropsychological tests by domain, with normative source utilized

Domain / Test	Normative Source
<i>Processing Speed</i>	
Trail Making Test Part A	(Tombaugh, 2004)
Digit Symbol Coding	(Wechsler, 1997b)
Symbol Search	
<i>Executive Function</i>	
Trail Making Test Part B	(Tombaugh, 2004)
Verbal Fluency (FAS)	(Tombaugh, Kozak, & Rees, 1999)
Verbal Fluency (Animals)	(Tombaugh, et al., 1999)
Ruff Figural Fluency Test	(Ruff, 1996)
Wisconsin Card Sorting Test – 64 Card	(Kongs, Thompson, Iverson, & Heaton, 2000)
<i>Working Memory</i>	
WAIS-III Digit Span	(Wechsler, 1997b)
WAIS-III Arithmetic	(Wechsler, 1997b)
WAIS-III Letter-Number Sequencing	(Wechsler, 1997b)
<i>Learning</i>	
CVLT-II Trial 1-5 Total	(Delis, Kramer, Kaplan, & Ober, 2000)
BVMT-R Trial 1-3 Total	(Benedict, 1997)
<i>Recall</i>	

CVLT-II Short Delay Free Recall	(Delis, et al., 2000)
CVLT-II Long Delay Free Recall	(Delis, et al., 2000)
BVMT-R Long Delay Free Recall	(Benedict, 1997)
Rey-Osterreith Complex Figure - Delayed Recall	(Meyers & Meyers, 1995)
<i>Motor Function</i>	
Grooved Pegboard Dominant Hand	(Bornstein, 1985)
Grooved Pegboard Non-dominant Hand	(Bornstein, 1985)

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